RESPONSE

I. Status of the Claims

Prior to the present paper, claims 40, 43-46, 52-64, 69, 70, 72, 74-76 and 78 were pending. Presently, claims 40, 43-46, 52-60, 62-64, 75, 76 and 78 have been amended without narrowing to more clearly define the invention. No claims have been canceled. Claims 79-81 have been added, which are unified with the examined claims and fully supported by the specification. Claims 40, 43-46, 52-64, 69, 70, 72, 74-76 and 78-81 are therefore in the case.

According to 37 C.F.R. § 1.121, and for the convenience of the Examiner, a clean copy of the pending claims is included (**Exhibit A**), along with a copy of the pending claims showing the present revisions (**Exhibit B**). The claims in each are marked "(Amended)" and "(New)" where appropriate.

II. Support for the Claims

Support for the revised and new claims is to be found throughout the specification and claims of the original and parent applications. In light of the claims canceled to date, no fees should be required for the additional claims. However, any fees deemed necessary should be deducted from Williams, Morgan & Amerson, P.C. Deposit Account No. 50-0786/4100.000582.

Claim 40 has been revised to clarify that the invention concerns methods for binding a "latent" transforming growth factor β (TGF-β) protein by contact with a purified mammalian LTBP-3 protein or polypeptide. This change even more clearly defines a stated and inherent feature of the invention, which is evident in that "LTBP-3" means Latent TGF-β Binding Protein-3. The revision is therefore supported by the claim itself and the entire specification (see *e.g.*, title and abstract), such as at pages 2-8, 44-48 and in Example I.

The remaining claim amendments also concern only revisions to recite methods for binding "latent" TGF-β. Such changes account for the amendments to each of claims 43-46, 52-60, 62-64, 75, 76 and 78, which even more clearly define a stated and inherent feature of the invention and are supported by the entire specification, as described above.

New claim 79 is presented in addition to claim 44, and more positively recites certain stated and inherent features of the invention. The claim is drawn to a method of binding "a latent complex of TGF-β", which comprises "mature TGF-β" and "latency associated peptide (LAP)", as supported by the specification at least at pages 2-8 (see page 7, line 21 to page 8, line 16); pages 44-48 and in Example I. The LTBP-3 is defined in the same structural terms and is characterized as binding to the recited latent complex of TGF-β.

Dependent claim 80 is a counterpart to claim 45, and is supported by claims 79 and 45, and by the specification, as described above.

Finally, claim 81 is provided in addition to claim 46, to more positively recite certain stated and inherent features of the invention. Claim 81 is drawn to a method of binding "a latent complex of TGFβ", which comprises "mature TGF-β" and "latency associated peptide (LAP)", as supported by the specification at least at pages 2-8 (see page 7, line 21 to page 8, line 16); pages 44-48 and in Example I. The LTBP-3 is defined in the same structural terms and is characterized as binding to LAP within the recited latent complex of TGF-β, which has particular support in the specification at least at page 8, lines 15-16.

It will therefore be understood that no new matter is included within any of the revised or new claims.

III. Specification, Drawings and Sequences

The Action at page 2 indicates that amendments to page 21 and page 75 could not be made. Applicants apologize for these inconsistencies, which are corrected herein.

The Action at page 2 further objects to the disclosure due to perceived informalities in Figures 7, 8, 9 and 10. In fact, there are no informalities as the referenced figures have been canceled from the application and the corresponding text removed from the specification. These changes are the same as entered in the parent application.

Although the parent and present application were filed with FIGS. 1 through 13, several figures were canceled as not necessary for one of ordinary skill in the art to make and use the claimed invention without undue experimentation in light of the present disclosure, and as redundant in light of the sequence listing. Accordingly, the parent and present application only contain FIGS. 1 through 8.

It appears that the Official Draftsman also reviewed the informal drawings (FIGS. 1-13), rather than the formal drawings (FIGS. 1-8) already submitted. A second version of formal drawings (FIGS. 1-8 on 8 sheets) has already been resubmitted (August 29, 2002).

The Action at page 3 continues to object to the specification based on a perceived failure to include sequence identifiers at each place where a sequence is discussed, with exemplary reference to Figure 8. As described above, there are no informalities - - as the figures containing the sequences were canceled as being redundant in light of the sequence listing.

To the extent that any informalities remained prior to the present paper, the formal drawings resubmitted on August 29, 2002 and the foregoing amendments to the specification perfect the disclosure. The application is therefore in complete compliance with the requirements for the specification, drawings and sequences.

The amendments to the specification comply with 37 C.F.R. § 1.121(b) as the amendments include unambiguous instructions; present new paragraphs in clean form in the amendment; and include another version of the replacement paragraphs, separate from the amendments, marked up to show all changes relative to the previous version of the paragraphs (**Exhibit C**).

IV. Priority

The Action at page 4 alleges that this application is not entitled to the priority date of application Serial No. 08/479,722 ("the '722 application). Applicants respectfully traverse.

The present application is properly entitled to the benefit of the filing date of the '722 application under 35 U.S.C. § 120 as the '722 application discloses the presently claimed invention in the manner provided by 35 U.S.C. § 112, first paragraph. Indeed, the Action has not provided any reasoning to support the position that priority is not proper.

The Action alleges that "support for the presently claimed invention cannot be found in the 08/479,722 parent application and the lack of such support raises the issue of new matter" (Action at page 4). In contrast, the support for the claims in the specification has been recited at all points during prosecution of the present application. As this application is a continuation of the '722 application, and the specification is therefore a *photocopy*, the support detailed is *prima facie* evidence that there are no new matter issues.

The priority issue therefore appears to be a re-statement of the 35 U.S.C. § 112, first paragraph rejection (although the § 112 rejection is based on a perceived lack of enablement, not written description or new matter). In any event, Applicants' response to the § 112, first paragraph rejection addresses all concerns under § 112, first paragraph, including written description and enablement.

V. Rejection of All Claims Under 35 U.S.C. § 112, First Paragraph

The Action at pages 4-6, first rejects all pending claims under 35 U.S.C. § 112, first paragraph as allegedly lacking enabling support in the specification. Although Applicants respectfully traverse, the Action's concerns are overcome.

The rejection draws Applicants' attention to the perceived imprecision in the claim language. Applicants appreciate the Action's attention to such issues (see page 6 in particular), and the opportunity to more precisely define the nature of the claimed invention.

As claimed in the parent application, now U.S. Patent No. 6,074,840 ("the '840 patent"), Applicants have provided novel and non-obvious Latent TGF-β Binding Proteins, termed LTBP-3 proteins or polypeptides, which are defined in structural and functional terms, including binding to TGF-β. The invention of the present application, in an overall sense, concerns methods of using these LTBP-3 proteins and polypeptides to bind TGF-β. However, as indicated in the Action, and evident in the definition of the claimed LTBP-3 (L for Latent), LTBP-3 binds to Latent TGF-β, *i.e.*, a latent complex of TGF-β that comprises mature TGF-β and latency associated peptide (LAP).

The original claim language was believed to be drafted in terms consistent with the enabling support in the specification, as would be understood by those of ordinary skill in the art. As the specification consistently teaches binding of "latent" TGF-β by the claimed "latent" TGF-β binding proteins, it would be illogical to read the claims as directed to binding TGF-β in forms other than as "latent TGF-β". As it is not the function of the claims to *exclude* inoperative embodiments, the claims were appropriately drafted. *Atlas Powder Co. v. E.I. DuPont de Nemours & Co.*, 224 USPQ 409 (Fed. Cir. 1984).

Nonetheless, the Action's insight that the claims could be misinterpreted is appreciated. In particular, the Action at page 6 comments that "the claims are viewed as encompassing the direct binding of LTBP-3 to mature, active TGF-β", but that LTBP-1 "does not bind directly to active TGF-β1", quoting Kanzaki *et al.* (*Cell*, 61:1051-1061, 1990). Despite the fact that it is not appropriate to view the claims, when read in light of the specification, as encompassing the direct binding of LTBP-3 to mature, active TGF-β, Applicants have taken the opportunity to perfect the claim language throughout.

All claims therefore now more precisely recite methods of binding latent TGF-β, and thus even better accord with the teaching in the specification. As it is indisputable that the Latent TGF-β Binding Proteins of the '840 patent and the present application bind to Latent TGF-β, as defined in all pending claims, the rejection is overcome.

It is well established that a patent need not teach, and preferably omits, what is well known in the art. *Hybritech Inc. v. Monoclonal Antibodies, Inc.*, 231 USPQ 81 (Fed. Cir. 1986). The nature of latent TGF-β as a latent complex comprising mature TGF-β and latency associated peptide (LAP) is well known in the art. The present invention contributes to the art novel and non-obvious binding proteins that interact with such latent complexes. The structural and functional features of the new LTBPs, and their interaction with latent TGF-β complexes, are defined in the claims. Although other known components of the latent complex, *i.e.*, mature TGF-β and LAP, do not need to be recited in the claims, Applicants also provide claims 79-81 in which such elements are positively recited. These claims even further emphasize the compliance with 35 U.S.C. § 112, first paragraph.

The claim language thus even better accords with the teaching of the specification, as summarized by the Action at page 6. To the extent that the Action at pages 4-5 discussed specific sections of the art and the present application, Applicants respond as follows.

The Action first cites Saharinen *et al.* (*EMBO J.*, 15(2):245-117, 1996) as disclosing that the association of TGF-β1-LAP with LTBP-1 is thought to occur only inside cells, and cites Saharinen *et al.*, 1996 at page 249, right column, first full paragraph (Action at page 4). The next sentence of Saharinen is contradictory, though, explaining that as the redox potential of the extracellular milieu is strongly in favor of disulfide bond formation, the 8-Cys repeat of LTBP-1 can exchange disulfide bonds between "optionally bound TGF-β" (Saharinen *et al.*, 1996, at page 249, right column, first full paragraph). Thus, extracellular LTBPs have the option of binding TGF-β by disulfide bonds, as taught in the present specification (see page 8, lines 15-16) and in Kanzaki *et al.*, 1990. The one sentence in Saharinen *et al.*, 1996 therefore does not indicate a lack of enablement for the claimed invention.

Yin *et al.* (*J. Biol. Chem.*, 270(17):10147-10160, 1995), an article published on behalf of the present inventors, is next cited as disclosing the co-expression of LTBP-3 with TGF-β1, the binding of LTBP-3 to LAP by a disulfide bond and the regulation of extracellular matrix production by assembly of latent complexes *then* targeting to specific connective tissues. These statements are in accordance with the present specification and the claimed invention and there is nothing therein to evidence a lack of enabling support for the invention as claimed.

The Action next cites Saharinen *et al.* (*Cytokine Growth Factor Rev.*, 10:99-117, 1999) as disclosing that the major fraction of secreted LTBPs does not contain TGF-β (Saharinen *et al.*, 1999 at page 101, left column, penultimate sentence), which the Action interprets as indicating that "free LTBP does not bind Action TGF-β" (Action at page 4). There is nothing in Saharinen

et al., 1999, or in the knowledge available in the art, to support the conclusion reached by the Action. Rather than meaning that "free LTBP does not bind Action TGF-β", Saharinen *et al.,* 1999 explains, "LTBPs thus evidently possess separate roles *in vivo* as structural proteins of the extracellular matrix and as TGF-β targeting molecules" (Saharinen *et al.,* 1999 at page 101, left column, last sentence; emphasis added). This is again consistent with the present specification, which teaches that LTBP may function as an extracellular structural protein capable of both regulating and targeting TGF-β activity (see pages 45-46, 57-58 and 71-74), and does not indicate a lack of enablement for the claimed invention.

The Action further states that the specification lacks guidance and working examples concerning binding TGF-β with LTBP-3 in the absence of co-expression of TGF-β and LTBP-3, and that there is nothing in the prior art of record teaching the skilled artisan how to bind TGF-β with an exogenous source of LTBP-3 (Action at page 5). In contrast, Kanzaki *et al.*, 1990, cited by the Action as showing that LTBPs do not bind directly to active TGF-β, teaches that LTBPs do bind to latent TGF-β complexes. Indeed, this is a central finding of the Kanzaki paper, supporting the characterization of the cloned protein as a latent TGF-β binding protein (later termed LTBP-1).

The studies to test the binding of LTBP-1 to active TGF-β and TGF-β within the latent complex are described in Kanzaki at pages 1056-1057. TGF-β was labeled with ^{125}I and separately incubated with purified LTBP-1 or the large latent TGF-β complex, after which any bound proteins were cross-linked and immunoprecipitated with an antibody to LTBP-1 (Kanzaki at pages 1056-1057). Although no binding of ^{125}I-labeled TGF-β to the free form of LTBP-1 (TGF-β1-BP) could be detected, ^{125}I-labeled TGF-β was cross-linked to the large latent TGF-β complex (Kanzaki at page 1057, left column). The authors explain:

"No binding of ^{125}I-labeled TGF-β1 to the free form of TGF-β1-BP was recorded. In contrast, ^{125}I-labeled TGF-β1 was cross-linked to the large latent TGF-β complex; bands of 50 kd, 90-100 kd, 150-160 kd, and 230-260 kd were found (Figure 7). The sizes of these components are the expected sizes of ^{125}I-labeled TGF-β1 (12.5 kd under reducing conditions) covalently coupled to one subunit of the N-terminal part of the TGF-β1 precursor (40 kd), a dimer of the precursor part (80 kd), TGF-β1-BP (125-160 kd), and all three of these components (about 210 kd), respectively (Miyazono et al., 1988)."

Kanzaki at page 1057, left column; emphasis added.

Thus, the specification and the prior art of record teach how to bind TGF-β with an exogenous source of LTBP-3.

Rather than supporting a lack of enablement, the Saharinen, Yin and Kanzaki articles therefore support Applicants' position that one of ordinary skill in the art can practice the claimed invention without undue experimentation in light of the present specification. The global enablement rejection is therefore overcome and should be withdrawn.

VI. Rejection of Claims 52-54 Under 35 U.S.C. § 112, First Paragraph

The Action at pages 5-6 implies a particular rejection of claims 52-54 under 35 U.S.C. § 112, first paragraph as allegedly lacking enabling support in the specification. Although Applicants respectfully traverse, the Action's concerns are overcome.

The Action states that the terms "regulates" and "modulates" encompass both increases and decreases in activity or activation and takes the position that the specification lacks guidance and working examples concerning simultaneously or individually achieving either in the absence of co-expression of TGF-β with LTBP-3 (Action at pages 5-6). To the extent that the rejection rests upon concerns regarding co-expression, as it seems to do, this is overcome by the foregoing response, including the evidence in Kanzaki showing binding of TGF-β to an LTBP in the absence of co-expression.

As to the binding of LTBP-3 to latent TGF-β "regulating" and "modulating" the activation of TGF-β and TGF-β activity, whether or not such terms include increases and decreases in activity or activation is not relevant to the issue of enabling support.

As detailed in the art cited by the Office, it is known that TGF-βs affect the growth, differentiation and morphology of cells and the regulation of extracellular matrix synthesis and proteolysis (Saharinen *et al.*, 1999, bridging pages 99-100). TGF-β is a growth suppressor of many cell types, especially cells of epithelial and endothelial origin, but stimulates the growth of mesenchymal cells (Saharinen *et al.*, 1999, at page 100, left column, first paragraph; emphases added). As TGF-β has different actions in different tissues, and as LTBP-3 contributes to the control of TGF-β by facilitating the assembly of latent complexes and targeting such complexes to specific connective tissues, claims drawn to the regulation or modulation of TGF-β activation or activity are not lacking in enabling support, but flow naturally from the practice of the invention.

The implied separate rejection of claims 52-54 under 35 U.S.C. § 112, first paragraph is therefore overcome and should be withdrawn.

VII. Rejection of Claims 52-54 Under 35 U.S.C. § 112, Second Paragraph

The Action at page 6 last rejects claims 52-54 under 35 U.S.C. § 112, second paragraph as allegedly being indefinite in the use of the terms "regulates" and "modulates". Although Applicants respectfully traverse, these concerns are also overcome.

Should "regulate" and "modulate" encompass increases and decreases in activity or activation, those of ordinary skill in the art would nonetheless understand these terms in light of the specification. It is the function of the specification, not the claims, to set forth operative parameters for the practice of the invention. *Ex parte Jackson*, 217 USPQ 804 (PTO Bd. App.

1982). In this case, the different effects of TGF-βs on different cells and tissues, and the contribution of LTBP-3 binding to the control of TGF-β, are known in the art and taught in the specification. Thus, the metes and bounds of the claims are not rendered unclear merely because of the presence of alternative language. *Ex parte Holt*, 19 USPQ2d 1211, 1214, (B.P.A.I. 1991).

Moreover, "regulates" and "modulates" are used according to their ordinary meaning, both in everyday usage and in the biotech arts, and there is nothing indefinite in this language. For example, Webster's Collegiate Dictionary defines the primary (non-musical) meaning of modulate as "to adjust to or keep in proper measure or proportion". Thus, LTBP-3 binding to latent TGF-β adjusts, or keeps in proper measure or proportion, the activation of TGF-β, which is consistent with the teaching of the specification.

In addition to their routine use in biotechnology, these terms are also used in the context of TGF-β biology, as evidenced by the papers cited by the Office. As examples, Saharinen *et al.*, 1996 states "transforming growth factor-βs (TGF-βs) are a family of multifunctional growth-modulating polypeptides, which affect the growth, differentiation and morphology of cells..." (Saharinen *et al.*, 1996, at page 245, left column, first sentence; emphasis added) and Saharinen *et al.*, 1999 explains that the effects of TGF-β on cell growth include suppression and stimulation in different cell types (see Saharinen *et al.*, 1999, page 100, left column, first paragraph). Thus, the cited art evidences the use of "modulates" to cover both increases and decreases.

As the terms regulates and modulates are sufficiently definite, the § 112, second paragraph rejection is therefore overcome and should be withdrawn.

VIII. Conclusion

This is a complete response to the referenced Official Action. In conclusion, Applicants submit that, in light of the foregoing remarks and enclosed documents, the present case is in condition for allowance and such favorable action is respectfully requested. Should Examiner Romeo have any questions or comments, or identify any informalities, a telephone call to the undersigned Applicants' representative is earnestly solicited.

Respectfully submitted,

Shelley P.M. Fussey, Ph.D.
Reg. No. 39,458
Agent for Applicant

WILLIAMS, MORGAN & AMERSON, P.C.
10333 Richmond, Suite 1100
Houston, Texas, 77042
(713) 934-4079

Date: December 13, 2002

EXHIBIT A
PENDING CLAIMS
U.S. Serial No. 09/592,685 (4100.000582; UM 926 P2C1)

40. (Thrice Amended) A method for binding a latent transforming growth factor β (TGF-β) protein in a sample, comprising contacting said sample with a purified mammalian LTBP-3 protein or polypeptide under conditions effective to allow binding of said LTBP-3 protein or polypeptide to said latent TGF-β protein; wherein said LTBP-3 protein or polypeptide specifically binds to latent TGF-β1 and exhibits at least 90% identity to the amino acid sequence of SEQ ID NO:4.

43. (Twice Amended) The method of claim 40, wherein said sample is located within an animal and said LTBP-3 protein or polypeptide is administered to said animal in an amount effective to bind latent TGF-β in said animal.

44. (Twice Amended) A method of binding latent TGF-β, comprising contacting a composition comprising latent TGF-β with a composition comprising a purified mammalian LTBP-3 protein or polypeptide in an amount effective to bind latent TGF-β; wherein said LTBP-3 protein or polypeptide specifically binds to latent TGF-β1 and exhibits at least 90% identity to the amino acid sequence of SEQ ID NO:4.

45. (Twice Amended) The method of claim 44, wherein said composition comprising latent TGF-β is located within an animal and said composition comprising said LTBP-3 protein or polypeptide is administered to said animal in an amount effective to bind latent TGF-β in said animal.

46. (Twice Amended) A method of binding latent TGF-β, comprising providing to an animal a composition comprising a purified mammalian LTBP-3 protein or polypeptide in an amount effective to bind latent TGF-β in said animal; wherein said LTBP-3 protein or polypeptide specifically binds to latent TGF-β1 and exhibits at least 90% identity to the amino acid sequence of SEQ ID NO:4.

52. (Twice Amended) The method of claim 46, wherein LTBP-3 binding to latent TGF-β regulates TGF-β activity in said animal.

53. (Twice Amended) The method of claim 46, wherein LTBP-3 binding to latent TGF-β modulates the activation of TGF-β in said animal.

54. (Twice Amended) The method of claim 46, wherein LTBP-3 binding to latent TGF-β modulates the activation of latent complexes that comprise TGF-β, thereby regulating TGF-β activity.

55. (Twice Amended) The method of claim 46, wherein LTBP-3 binding to latent TGF-β targets TGF-β to the extracellular matrix in said animal.

56. (Twice Amended) The method of claim 46, wherein LTBP-3 binding to latent TGF-β targets TGF-β to the bone matrix in said animal.

57. (Twice Amended) The method of claim 46, wherein LTBP-3 binding to latent TGF-β targets TGF-β to connective tissues in said animal.

58. (Twice Amended) The method of claim 46, wherein LTBP-3 binding to latent TGF-β targets TGF-β to the cell surface of cells in said animal.

59. (Twice Amended) The method of claim 46, wherein LTBP-3 binding to latent TGF-β protects latent TGF-β from proteolytic attack and activation in said animal.

60. (Twice Amended) The method of claim 46, wherein LTBP-3 binding to latent TGF-β protects latent TGF-β from proteolytic attack and activation during wound repair or tissue healing in said animal.

61. (Amended) The method of claim 46, wherein said LTBP-3 protein or polypeptide is a recombinant protein or polypeptide prepared by expressing an LTBP-3-encoding DNA segment in a recombinant host cell and purifying the expressed LTBP-3 protein or polypeptide away from total recombinant host cell components.

62. (Twice Amended) The method of claim 46, wherein said latent TGF-β is located within a tissue healing, wound repair tissue site or bone progenitor tissue site of said animal and wherein said LTBP-3 protein or polypeptide is provided to said tissue site.

63. (Amended) The method of claim 62, wherein said latent TGF-β is located within a tissue healing or wound repair tissue site of said animal.

64. (Amended) The method of claim 62, wherein said latent TGF-β is located within a bone progenitor tissue site of said animal.

69. (Amended) The method of claim 46, wherein said LTBP-3 protein or polypeptide comprises at least about thirty contiguous amino acids present in SEQ ID NO:4.

70. (Amended) The method of claim 46, wherein said LTBP-3 protein or polypeptide comprises at least about fifty contiguous amino acids present in SEQ ID NO:4.

72. (Amended) The method of claim 46, wherein said LTBP-3 protein or polypeptide exhibits between 91% and about 99% identity to the amino acid sequence set forth in SEQ ID NO:4.

74. (Amended) The method of claim 46, wherein said LTBP-3 protein or polypeptide comprises the amino acid sequence of SEQ ID NO:4.

75. (Twice Amended) A method of binding latent TGF-β within an extracellular matrix or connective tissue site of an animal, comprising contacting said tissue site with a purified mammalian LTBP-3 protein or polypeptide in an amount effective to bind latent TGF-β in said animal; wherein said LTBP-3 protein or polypeptide specifically binds to latent TGF-β1 and exhibits at least 90% identity to the amino acid sequence of SEQ ID NO:4.

76. (Twice Amended) A method of binding latent TGF-β within a repair or bone progenitor tissue site of an animal, comprising contacting said tissue site with a purified mammalian LTBP-3 protein or polypeptide in an amount effective to bind latent TGF-β in said animal; wherein said LTBP-3 protein or polypeptide specifically binds to latent TGF-β1 and exhibits at least 90% identity to the amino acid sequence of SEQ ID NO:4.

78. (Twice Amended) A method of binding latent TGF-β, comprising administering to an animal a composition comprising a purified mammalian LTBP-3 protein or polypeptide in an amount effective to bind latent TGF-β in said animal; wherein said LTBP-3 protein or polypeptide binds latent TGF-β and comprises at least fifteen contiguous amino acids present in SEQ ID NO:4 and exhibits at least 90% identity to the amino acid sequence set forth in SEQ ID NO:4.

79. (New) A method of binding a latent complex of TGF-β that comprises mature TGF-β and latency associated peptide (LAP), said method comprising contacting a composition comprising said latent complex of TGF-β with a composition comprising a purified mammalian LTBP-3 protein or polypeptide in an amount effective to bind to said latent complex of TGF-β; wherein said LTBP-3 protein or polypeptide specifically binds to latent TGF-β1 and exhibits at least 90% identity to the amino acid sequence of SEQ ID NO:4.

80. (New) The method of claim 79, wherein said composition comprising said latent complex of TGF-β is located within an animal and said composition comprising said LTBP-3 protein or polypeptide is administered to said animal in an amount effective to bind to said latent complex of TGF-β in said animal.

81. (New) A method of binding a latent complex of TGF-β that comprises mature TGF-β and latency associated peptide (LAP), said method comprising providing to an animal a composition comprising a purified mammalian LTBP-3 protein or polypeptide in an amount effective to bind to LAP in a latent complex of TGF-β in said animal; wherein said LTBP-3 protein or polypeptide binds to LAP in said latent complex of TGF-β and exhibits at least 90% identity to the amino acid sequence of SEQ ID NO:4.

EXHIBIT B
PENDING CLAIMS
U.S. Serial No. 09/592,685 (4100.000582; UM 926 P2C1)

40. (Thrice Amended) A method for binding a latent transforming growth factor β (TGF-β) protein in a sample, comprising contacting said sample with a purified mammalian LTBP-3 protein or polypeptide under conditions effective to allow binding of said LTBP-3 protein or polypeptide to said latent TGF-β protein; wherein said LTBP-3 protein or polypeptide specifically binds to latent TGF-β1 and exhibits at least 90% identity to the amino acid sequence of SEQ ID NO:4.

43. (Twice Amended) The method of claim 40, wherein said sample is located within an animal and said LTBP-3 protein or polypeptide is administered to said animal in an amount effective to bind latent TGF-β in said animal.

44. (Twice Amended) A method of binding latent TGF-β, comprising contacting a composition comprising latent TGF-β with a composition comprising a purified mammalian LTBP-3 protein or polypeptide in an amount effective to bind latent TGF-β; wherein said LTBP-3 protein or polypeptide specifically binds to latent TGF-β1 and exhibits at least 90% identity to the amino acid sequence of SEQ ID NO:4.

45. (Twice Amended) The method of claim 44, wherein said composition comprising latent TGF-β is located within an animal and said composition comprising said LTBP-3 protein or polypeptide is administered to said animal in an amount effective to bind latent TGF-β in said animal.

46. (Twice Amended) A method of binding latent TGF-β, comprising providing to an animal a composition comprising a purified mammalian LTBP-3 protein or polypeptide in an amount effective to bind latent TGF-β in said animal; wherein said LTBP-3 protein or polypeptide specifically binds to latent TGF-β1 and exhibits at least 90% identity to the amino acid sequence of SEQ ID NO:4.

52. (Twice Amended) The method of claim 46, wherein LTBP-3 binding to latent TGF-β regulates TGF-β activity in said animal.

53. (Twice Amended) The method of claim 46, wherein LTBP-3 binding to latent TGF-β modulates the activation of TGF-β in said animal.

54. (Twice Amended) The method of claim 46, wherein LTBP-3 binding to latent TGF-β modulates the activation of latent complexes that comprise TGF-β, thereby regulating TGF-β activity.

55. (Twice Amended) The method of claim 46, wherein LTBP-3 binding to latent TGF-β targets TGF-β to the extracellular matrix in said animal.

56. (Twice Amended) The method of claim 46, wherein LTBP-3 binding to latent TGF-β targets TGF-β to the bone matrix in said animal.

57. (Twice Amended) The method of claim 46, wherein LTBP-3 binding to latent TGF-β targets TGF-β to connective tissues in said animal.

58. (Twice Amended) The method of claim 46, wherein LTBP-3 binding to latent TGF-β targets TGF-β to the cell surface of cells in said animal.

59. (Twice Amended) The method of claim 46, wherein LTBP-3 binding to latent TGF-β protects latent TGF-β from proteolytic attack and activation in said animal.

60. (Twice Amended) The method of claim 46, wherein LTBP-3 binding to latent TGF-β protects latent TGF-β from proteolytic attack and activation during wound repair or tissue healing in said animal.

61. (Amended) The method of claim 46, wherein said LTBP-3 protein or polypeptide is a recombinant protein or polypeptide prepared by expressing an LTBP-3-encoding DNA segment in a recombinant host cell and purifying the expressed LTBP-3 protein or polypeptide away from total recombinant host cell components.

62. (Twice Amended) The method of claim 46, wherein said latent TGF-β is located within a tissue healing, wound repair tissue site or bone progenitor tissue site of said animal and wherein said LTBP-3 protein or polypeptide is provided to said tissue site.

63. (Amended) The method of claim 62, wherein said latent TGF-β is located within a tissue healing or wound repair tissue site of said animal.

64. (Amended) The method of claim 62, wherein said latent TGF-β is located within a bone progenitor tissue site of said animal.

69. (Amended) The method of claim 46, wherein said LTBP-3 protein or polypeptide comprises at least about thirty contiguous amino acids present in SEQ ID NO:4.

70. (Amended) The method of claim 46, wherein said LTBP-3 protein or polypeptide comprises at least about fifty contiguous amino acids present in SEQ ID NO:4.

72. (Amended) The method of claim 46, wherein said LTBP-3 protein or polypeptide exhibits between 91% and about 99% identity to the amino acid sequence set forth in SEQ ID NO:4.

74. (Amended) The method of claim 46, wherein said LTBP-3 protein or polypeptide comprises the amino acid sequence of SEQ ID NO:4.

75. (Twice Amended) A method of binding latent TGF-β within an extracellular matrix or connective tissue site of an animal, comprising contacting said tissue site with a purified mammalian LTBP-3 protein or polypeptide in an amount effective to bind latent TGF-β in said animal; wherein said LTBP-3 protein or polypeptide specifically binds to latent TGF-β1 and exhibits at least 90% identity to the amino acid sequence of SEQ ID NO:4.

76. (Twice Amended) A method of binding latent TGF-β within a repair or bone progenitor tissue site of an animal, comprising contacting said tissue site with a purified mammalian LTBP-3 protein or polypeptide in an amount effective to bind latent TGF-β in said animal; wherein said LTBP-3 protein or polypeptide specifically binds to latent TGF-β1 and exhibits at least 90% identity to the amino acid sequence of SEQ ID NO:4.

78. (Twice Amended) A method of binding latent TGF-β, comprising administering to an animal a composition comprising a purified mammalian LTBP-3 protein or polypeptide in an amount effective to bind latent TGF-β in said animal; wherein said LTBP-3 protein or polypeptide binds latent TGF-β and comprises at least fifteen contiguous amino acids present in SEQ ID NO:4 and exhibits at least 90% identity to the amino acid sequence set forth in SEQ ID NO:4.

79. (New) A method of binding a latent complex of TGF-β that comprises mature TGF-β and latency associated peptide (LAP), said method comprising contacting a composition comprising said latent complex of TGF-β with a composition comprising a purified mammalian LTBP-3 protein or polypeptide in an amount effective to bind to said latent complex of TGF-β; wherein said LTBP-3 protein or polypeptide specifically binds to latent TGF-β1 and exhibits at least 90% identity to the amino acid sequence of SEQ ID NO:4.

80. (New) The method of claim 79, wherein said composition comprising said latent complex of TGF-β is located within an animal and said composition comprising said LTBP-3 protein or polypeptide is administered to said animal in an amount effective to bind to said latent complex of TGF-β in said animal.

81. (New) A method of binding a latent complex of TGF-β that comprises mature TGF-β and latency associated peptide (LAP), said method comprising providing to an animal a composition comprising a purified mammalian LTBP-3 protein or polypeptide in an amount effective to bind to LAP in a latent complex of TGF-β in said animal; wherein said LTBP-3 protein or polypeptide binds to LAP in said latent complex of TGF-β and exhibits at least 90% identity to the amino acid sequence of SEQ ID NO:4.